Niemann-Pick Disease (NPD) is a rare autosomal recessive lysosomal lipid storage disorder. The disease is caused by gene mutations that affect the metabolism of sphingolipids. The dysfunctions cause sphingomyelin to accumulate in different organs. NPD includes forms with low and high levels of sphingomyelin. We report a case of a 34-year-old man with a family history of NPD type B who presented with hepatosplenomegaly, neurological deficiency, bone abnormalities, and myositis ossificans. The clinical, biochemical, and imaging data confirmed the combined diagnosis of NPD type B with myositis ossificans.

**Keywords:** Myositis ossificans; Niemann-Pick; Sphingolipids.

**INTRODUCTION**

Niemann-Pick Disease (NPD) is a rare autosomal recessive lysosomal lipid storage disorder. The disease was first described by Albert Niemann in 1914 and then characterized pathologically by Ludwig Pick in 1927\(^1\). NPD is subdivided into six types. NPD types A and B are caused by mutations in the sphingomyelin phosphodiesterase 1 gene (SMPD-1) that cause a deficiency in the enzyme acid sphingomyelinase (ASM). ASM is found in the lysosomes and is necessary to metabolize the lipid sphingomyelin. If ASM is not properly functioning or is absent, sphingomyelin cannot be metabolized properly and accumulates within cells, causing cell death and malfunctions of major organ systems.

NPD types C1 and C2 are caused by mutations in the genes NPC1 and NPC2, which affect the intracellular processing, and transportation of cholesterol and glycolipid and cause the accumulation of lipids in the brain and body. NPD type D is an allelic variant of NPD type C that shares a specific point mutation in the NPC1 gene\(^2\).

NPD types E and F are rare forms of the disease that have not been well characterized. Only a few cases have been described in the literature. NPD type E is an indeterminate adult form with moderate hepatosplenomegaly (HSM) and some increase of sphingomyelin in the liver, spleen and bone marrow. Type F has a childhood onset with splenomegaly, lack of neurological involvement, diminished ASM activity and thermolabile enzyme\(^3,4\).

Before the molecular defects responsible for NPD were described, the disease had been separated in two types, I and II, denoting the forms of the disease that involve high (A and B) and low (C and D) levels of the lipid sphingomyelin, respectively.

The following is a summary of the six types of NPD described to date:

- **type A:** acute neuronopathic form, usually fatal in childhood;
- **type B:** visceral form;
- **type C:** chronic neuronopathic form, characterized by slow progression of central nervous system degradation;
- **type D:** Nova Scotia variant;
- **type E:** adult, non-neuronopathic form;
- **type F:** sea-blue histiocyte disease\(^5\).

Case reports with subacute forms of NPD have also been described in the literature, later identified as representing the clinical course of NPD type C\(^6\).

The incidence of both NPD types A and B is estimated to be 1 in 250,000 individuals, with a higher occurrence in Ashkenazi Jews\(^7\). The clinical presentations of NPD types A and B range from severe neurological de-
generation resulting in death between the age of two and four (type A), to a variable clinical course and prognosis with a comparatively long lifespan (type B). Patients with NPD type B usually present with HSM, pulmonary involvement - in the form of diffuse reticular or finely nodular involvement, pancytopenia caused by hypersplenism, occasionally seen cherry-red spot in the macula, bone changes, and neurological involvement with most commonly peripheral neuropathy and learning disabilities⁸⁻¹⁰. The results of many studies show a possibility for prenatal diagnosis of NPD type B¹⁰.

As a result of bone changes and neurological impairments, patients with NPD are often exposed to physical trauma. Such trauma could be a possible causative factor for heterotropic bone formations in the context of myositis ossificans. The latter represents a very rare progressive disorder with unknown pathogenesis causing calcification of muscles, tendons, and ligaments¹¹.

In this publication, we report the first case, to our knowledge, of NDP type B associated with myositis ossificans.

CASE REPORT

A 34-year-old man of Roma ethnicity was admitted in the rheumatology clinic with a seven-month history of walking difficulties, muscle and tendon weakness, mechanically-induced pain in the pelvic area, limited motion in the hip joints with pain radiating down the right leg to the knee, morning stiffness lasting over one hour, and an inability to relieve symptoms with non-steroidal anti-inflammatory drugs. The patient was the third child in his family, born after a normal pregnancy. He did not learn to walk and did not start to talk until the age of two. Also at age two, the patient was diagnosed with HSM. When he reached school age, the patient had psychomotor retardation with an apparent deterioration in neurological development when compared to his peers.

The patient’s family history included a brother who had died at an early age after a prolonged pneumonia, a deceased sister with a history of asthma, a brother with HSM, and a cousin with NPD type B.

Five years before presentation, the patient had been diagnosed with paranoid schizophrenia and bipolar affective disorder. The patient was treated with clozapine.

The physical examination of the patient showed a dysmorphic face with gothic palatum, bilateral ophthalmoplegia, a pulse rate of 84 beats per minute, and blood pressure of 90/60 mmHg. The patient was afebrile. He had a chest deformity presenting with thoracic scoliosis and expiratory wheezing with otherwise normal vesicular breath sounds. His respiratory rate was 18 breaths per minute.

The examination of the abdomen revealed HSM – on palpation, the liver was enlarged up to 3 cm, and the spleen up to 8 cm below the costal margin. Both organs were not tender. The patient had difficulty walking on his own, had limited motion in the hip joints with cam deformity of the right femoral head, and an internal rotation of the right hip joint. He also reported pain and limited motion in the right knee joint with a flexion contracture at 45˚, and pain and limited motion in the lumbar spine (the finger-floor distance was 60 cm).

The examination of the nervous system revealed evidence of various lesions: cerebellar syndrome with ataxia; spastic gait; intentional tremor of all extremities; adiadochokinesis; quadripyramidal syndrome with lower limb spasticity; enlarged reflex zones; and bilateral pathological reflexes (Babinski sign, Gordon and Oppenheim reflexes). The patient had no abdominal reflexes. Other findings included: polyneuropathy syndrome; lumbovertebral syndrome with increased tone of the paravertebral musculature; and cognitive dysfunction.

The magnetic resonance imaging (MRI) of the central nervous system showed dilated subarachnoid spaces in the brain convex of the frontal and subtemporal areas bilaterally. There were several zones of increased intensity on the T2-weighted images, which were localized in the supratentorial periventricular white matter of the parieto-occipital areas bilaterally. There was mild atrophy of the cerebellar hemispheres with dilated interfoliar sulci.

The ophthalmological examination showed changes suggestive of persistent hyperplastic primary vitreous (also known as persistent fetal vasculature) bilaterally, representing an inherited anomaly. The exam further revealed impaired eye movements characterized by initial vertical saccadic difficulties and normal horizontal saccades.

The blood tests revealed: thrombocytopenia (PLT – 73x10^9/L); leukocytes on the low reference range (WBC – 3.5x10^9/L), without abnormalities in the WBC differential count; and acid phosphomocerollase (ASM) activity of 2.7 (reference range 21–143). The remaining blood tests (erythrocyte sedimentation rate, C-reactive
protein, red blood cell count, hemoglobin level, glucose, creatinine, uric acid, liver enzymes; creatine phosphokinase (CPK), cholesterol, bilirubin, calcitonin, parathormone, α-fetoprotein, calcium and phosphorus levels) were within the reference ranges.

The urine tests showed protein trace with 10-12 erythrocytes and 10-12 leukocytes in the urinary sediment. The 24-hour diuresis was 1500 ml with protein concentration of 0.36 g/L and proteinuria of 0.54 g/24h.

The chest radiography showed denser hilus and a reticular interstitial pattern of lung involvement (Figure 1).

The abdominal ultrasound showed HSM, normal liver echo structure and increased renal parenchymal echogenicity bilaterally that was suggestive for glomerular disease. The patient refused percutaneous kidney biopsy intended to determine the type of kidney damage.

On bone and joints radiographs massive ossifications with amorphous character around the hip joints were seen (Figure 2) with right hip joint in internal rotation leading to internal rotation in the knee joint (Figure 3). Hip and knee joints had otherwise normal joint spaces. The ankle joints had normal joint space, the foot arches were high, and there was a heel-spur on the right site.

The computed tomography (CT) images of the pelvic area (Figure 4, Figure 5) showed multiple massive ossifications and exostoses around the iliac bones and greater trochanter bilaterally. The ossifications were also visible in the internal and external obturator muscles and the gluteus medius and minimus, and were more severe in the quadratus femoris muscle. The images were suggestive for myositis ossificans.

The severity of the heterotopic ossification around
the hip joints and the iliac bone suggested that it had been caused by repeated trauma. A consultation with an orthopedic surgeon was made about the possibility of debridement of the abnormal tissue.

**CONCLUSION**

Several case reports of NPD type B in adults can be found in the literature, characterized by haematological abnormalities (thrombocytopenia)\(^7,12\), bone-marrow abnormalities (sea-blue histiocytes)\(^13\), pulmonary abnormalities (bronchopneumonia, unexplained diffuse endogenous lipid pneumonia, diffuse infiltrative damage, lung affection with a “crazy-paving” image)\(^14-16\), hepatic abnormalities (cirrhosis and portal hypertension)\(^17\), ocular abnormalities (macular cherry-red spot, mild myopia, a mild generalized colour abnormality, visual impairment, ophthalmoplegia)\(^18\), endocrine abnormalities (polyglandular involvement such as partial adrenal insufficiency), dermatological abnormalities (idiopathic nodular panniculitis) and abnormalities in the musculoskeletal system (arthralgias, bone pain, osteopenia, osteoporosis, vertebral fractures)\(^12,16\).

To the best of our knowledge this is the first case report of NPD type B associated with myositis ossificans described in the literature. The diagnosis of NPD type B in this patient was based on his family history of two deceased siblings and a cousin with NPD type B disease; laboratory results showing decreased ASM activity; HSM diagnosed in childhood; cognitive dysfunction; mild neurological retardation; bipolar affecting disorder; central nervous system abnormalities revealed on the MRI images; diffuse reticular pulmonary involvement of the lung; thrombocytopenia caused by hypersplenism; and the presence of bone abnormalities. The diagnosis of myositis ossificans was established based on the typical images on the X-ray and CT.

The pathophysiological mechanism underlying the new extrasosseous bone formation in this patient with NPD type B was unclear. As a result of infiltration of the affected organs with abnormal storage material the bony changes in NPD are characterized by slowed mineralization of the bone and long-bone expansion with modeling defects. In association with local trauma this could serve as a possible predisposing factor for soft tissue calcification. The localization of the myositis ossificans in the internal and external obturator muscles, the gluteus medius and minimus, and the quadratus femoris muscles in our patient supported the possible role of the repetitive trauma as a causative or aggravating factor for this condition. The systemic factors were excluded by the absence of metabolic abnormalities (lipid profile, uric acid) and a normal CPK value.

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